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International survey of neuromonitoring and neurodevelopmental outcome in children and adults supported on extracorporeal membrane oxygenation in Europe

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Abstract

Background: Adverse neurological events during extracorporeal membrane oxygenation (ECMO) are common and may be associated with devastating consequences. Close monitoring, early identification and prompt intervention can mitigate early and late neurological morbidity. Neuromonitoring and neurocognitive/neurodevelopmental follow-up are critically important to optimize outcomes in both adults and children.

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Objective: To assess current practice of neuromonitoring during ECMO and neurocognitive/neurodevelopmental follow-up after ECMO across Europe and to inform the development of neuromonitoring and follow-up guidelines.
Methods: The EuroELSO Neurological Monitoring and Outcome Working Group conducted an electronic, web-based, multi-institutional, multinational survey in Europe.
Results: Of the 211 European ECMO centres (including non-ELSO centres) identified and approached in 23 countries, 133 (63%) responded. Of these, 43% reported routine neuromonitoring during ECMO for all patients, 35% indicated selective use, and 22% practiced bedside clinical examination alone. The reported neuromonitoring modalities were NIRS (n = 88, 66.2%), electroencephalography (n = 52, 39.1%), transcranial Doppler (n = 38, 28.5%) and brain injury biomarkers (n = 33, 24.8%). Paediatric centres (67%) reported using cranial ultrasound, though the frequency of monitoring varied widely. Before hospital discharge following ECMO, 50 (37.6%) reported routine neurological assessment and 22 (16.5%) routinely performed neuroimaging with more paediatric centres offering neurological assessment (65%) as compared to adult centres (20%). Only 15 (11.2%) had a structured longitudinal follow-up pathway (defined followup at regular intervals), while 99 (74.4%) had no follow-up programme. The majority (n = 96, 72.2%) agreed that there should be a longitudinal structured follow-up for ECMO survivors.
Conclusions: This survey demonstrated significant variability in the use of different neuromonitoring modalities during and after ECMO. The perceived importance of neuromonitoring and follow-up was noted to be very high with agreement for a longitudinal structured follow-up programme, particularly in paediatric patients. Scientific society endorsed guidelines and minimum standards should be developed to inform local protocols.

Keywords
neurological outcomes; neuropsychological; neurocognitive; longitudinal pathway; long-term follow-up; brain function; mechanical circulatory support

Background

An increasing number of adults and children with potentially reversible cardiac or pulmonary failure refractory to conventional therapies are now being offered extracorporeal membrane oxygenation (ECMO), as evidenced by the recent SARS-CoV-2 pandemic (https://www.euroelso.net/covid-19/covid-19-survey).[1] Adverse neurological events during ECMO are frequently reported in children and adults, with a devastating impact on patient outcome.[2–12] While multiple factors can account for such adverse events on ECMO, there are few that can be modified. A systematic review of 44 studies of adults supported on ECMO reported that the median frequency of acute neurologic complications was 13% (range 1–78%), including intracranial haemorrhages (5%), ischaemic strokes (5%) and seizures (2%), with an associated mortality of 96%, 84% and 40%, respectively.[2] Furthermore, a higher incidence (83%) of hypoxic ischaemic encephalopathy in patients with neurologic complications (vs 42% in those without), leading to brain death in over 50% of cases was also reported.[2] Interestingly, no study described daily neurological assessments or coagulation monitoring, both of which can have an impact on the incidence and severity of these neurological events.[2] Several reports from the Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI, USA) Registry have described the incidence and survival from neurological complications.[1,3,6,13,14] Polito et al.[3] reported that up to 20% of neonates supported on ECMO developed neurological complications, while a slightly reduced rate (15%) was reported in adults.[6] Minimizing neurological complications on ECMO is crucial as these are associated with high in-hospital morbidity and mortality as well as long-term neurocognitive deficits in adults and children.[15,16] Identifying neurological complications early before clinical signs manifest, can be challenging and is subject to institutional variations in neuromonitoring protocols; as an example, early routine neuroradiology has been reported to identify a higher rate of intracranial haemorrhage with substantially improved overall outcome.[17] In addition, lack of standardization of reporting of neurological outcomes leads to variability in published literature.[18,19]

As the application of extracorporeal cardiopulmonary resuscitation (ECPR) increases worldwide, a higher proportion of survivors with significant neurological sequelae are likely to need support.[20–22] In an ELSO Registry study on 695 children supported with ECPR, Thiagarajan et al.[14] reported seizures in 11.9%, radiologic evidence of infarct or haemorrhage in 11.6%, and brain death in 10.6%. Similarly, large non-randomized studies in adult ECPR patients demonstrated variable neurological outcome both for in-hospital and out-of-hospital cardiac arrests with significant adverse long-term neurocognitive sequelae.[23–26] While the ELSO Registry provides data on the neurological complications on ECMO in different age groups and indications, these are dependent on self-reporting, and influenced by variability in definitions of neuro-injury and neuromonitoring protocols.[18] Furthermore, this valuable

dataset does not include data on neurological morbidity at follow-up.

Data on neurocognitive outcomes on long-term follow-up of ECMO survivors is limited, particularly in adults.[27–30] Some studies have reported that 41% adult ECMO survivors have impaired neuropsychological performance as well as high levels of distress, physical aggression, anger and alexithymic traits.[28–30] Long-term follow-up in children has indicated that a proportion of children develop neuropsychological deficits leading to learning difficulties at school which in some cases become apparent with increasing age.[31–33] Ijsselstijn et al.[31,34] have reported increasing motor and executive function impairments later in life in neonatal ECMO survivors. Therefore, developing and establishing guidelines endorsed by scientific societies to standardize neuromonitoring and neuro follow-up of ECMO patients is central to optimizing patient outcomes.

The aim of this international survey was to analyse the current practice of neurological monitoring during ECMO and neurocognitive follow-up after ECMO across institutions in Europe with a view to identify the requirement for standardizing of neurological monitoring methods during ECMO and propose a framework for longitudinal long-term neurodevelopmental outcome after ECMO.

Methods

Development of the survey

To study the above aim, the EuroELSO Neurological Monitoring and Outcome Working Group conducted a multi-institutional, multi-national survey and a draft endorsed by EuroELSO was piloted at the EuroELSO conference in Glasgow in 2016. This led to the development of a detailed survey with input from specialists from adult and paediatric ECMO units. The list of ECMO centres (including non-ELSO centres) in Europe was populated from the ELSO Directory as well as from individual country representatives who disseminated the survey to ECMO centres. As this was a quality improvement survey, ethical approval was waived.

Design of the survey

The survey was designed using SurveyMonkey software (SurveyMonkey Inc., San Mateo, California, USA) containing 49 questions (Additional File 1, Supplemental Digital Content 1, https://www.surveymonkey.co.uk/r/H9CMWWZ). The survey comprised of four essential sections – (1) Basic information about the ECMO centre and institution covering demographic data, (2) Routine neuromonitoring (could include an intermittent or continuous modality) during ECMO (in addition to bedside neurological assessment) regardless of whether the patient has sustained a neurological insult or not, (3) Neurological assessment (physician or neurologist) post-ECMO and/or any neuroimaging done post-ECMO but pre-discharge from the ECMO institution and (4) Neurodevelopmental/neuropsychological follow-up post discharge asking centres to provide details if they had a programme and if they did not have a programme, to provide their considerations for an 'ideal' follow-up programme. The survey style included a mixture of multiple choice and open-ended (free text) questions with a drop-down menu of answers. The survey, once designed, was sent to an independent expert – Dr Melania Bembea, Johns Hopkins Medical Centre, Baltimore, Maryland, USA, for critical review. Following feedback, the survey underwent revision and further testing by the Working Group representatives from different countries within the EuroELSO and then accepted for distribution.

Distribution of the survey

In total, 211 ECMO centres were identified in 23 countries in Europe. The EuroELSO Neurological Monitoring and Outcome Survey was electronically sent to the Director and the ECMO co-ordinator of each centre. Only one response was expected per centre and respondents were advised to put together a consensus response. In the event of no response, reminder was sent after 2 weeks, and after 4 weeks, direct contact was established by phone requesting a response.

Data analysis

Data were exported from Survey Monkey software in a CSV file format into Microsoft Excel for Mac (Washington, USA, Version 16.35). Overall data are described in frequency and percentage. Analysis was descriptive with data divided into centres that treated paediatric, adult or mixed (adult and paediatric) patient populations, and into low-volume ($<$30/year) and high-volume ($>$30/year) centres. Correlations between responses from centres grouped as per patient population and volume were evaluated using Pearson's Chi square and Cramer's V test.

Results

Of the 211 European ECMO centres identified in 23 countries and approached, 133 (63%) centres responded to the survey.

Basic demographics about the ECMO centre and institution

Of these 133 respondents, 58 (44%) centres managed only adult patients, 40 (30%) managed paediatric

patients including neonates, and 35 (26%) treated both adults and children. The respondents comprised of ECMO programme Director (n = 73), lead ECMO Co-ordinator (n = 32) and senior ECMO physicians (n = 28). The distribution of the countries within Europe appeared well represented among the respondents with a lower response rate in Germany (38/74, 53%) and France (14/44, 32%). Of the 133 ECMO centres, 89 (67%) were ELSO Registry members, 33 (25%) were not and in 11 (8%) this information was unknown. The annual ECMO centre volume ranged from <10 to >100/year. The majority, (56, 42%) treated 10–30 patients/year; 25 (19%) treated 30–50, 22 (17%) treated 50–100 and 12 (9%) treated <10 patients/year. Eleven ECMO centres (8%) treated >100 patients annually, and six centres did not report their data. Almost all (126; 95%) treated both cardiac and respiratory failure, except seven that offered ECMO only for cardiac failure; and ECPR was provided in 101 (75%) and 74 (56%) had a heart and/or lung transplant bridging programme.

Routine neuromonitoring during ECMO

Of the 119 centres who responded to this question, 105 centres (88%) performed routine neuromonitoring during ECMO (57 for *all* patients and 48 for *selected* patients), whereas 14 responded that they conduct routine bedside clinical examination to assess the neurological state. The 48 respondents (43 adult centres) that monitored selected patients only identified ECPR (n = 31), veno-arterial (VA) ECMO (n = 21), acute neurological event (ANE: for example, seizure, abnormal movements, focal neurological deficits, infarct or bleed on neuroimaging, n = 27) and manipulations of the circuit (n = 4) as select indications for neuromonitoring. The 14 respondents who selected bedside clinical examination indicated that they would monitor ECMO patients following VA ECMO, ECPR, or ANE.

Mode of routine neuromonitoring on ECMO

The most common neuromonitoring modality reported was near-infrared spectroscopy (NIRS) used in two thirds (n = 88, 66%), followed by intermittent electroencephalography (EEG) (n = 52, 39%), transcranial Doppler (TCD) (n = 38, 28%), serum biomarkers of brain injury (n = 33, 25%), amplitude-integrated electroencephalography (aEEG) (n = 23,17%), evoked potentials (n = 20, 15%), continuous EEG (n = 19, 14%) and carotid Doppler (n = 8, 6%). Of the 58 adult centres, 28 used NIRS (48%), followed by EEG (40%) and one-third used biomarkers, particularly S-100B and Neuron Specific Enolase (NSE). Of the 40 paediatric centres, 32 (80%) used NIRS and the majority used it throughout the ECMO course, 29 (73%) used cranial ultrasound scan (USS) with variable frequency, intermittent EEG by 14 (35%) and aEEG by 48%, whereas continuous EEG was used by 10% of the respondents. A similar response was noted in the centres that managed both adult and paediatric patients: NIRS, cranial USS and intermittent EEG were most commonly used modalities. Cranial USS was reported to be used in 48/75 (64%) centres managing children; 19 (25%) reported daily, 15 (20%) twice weekly and 13 (17%) thrice weekly, and 11 (15%) would perform only if clinical concerns. Only 15 (11%) respondents reported routine use of brain CT, majority 98 (74%) reported undertaking brain CT only if clinical concerns of neurological problems. Reconstruction of vessels at decannulation was reported by 85 (64%) respondents: routinely in all (n = 38), and only in selected patients (n = 47). Routine use and timing of the different neuromonitoring modalities are described in Tables 1 and 2. Figure 1 shows the responses from the different countries in different regions of Europe.

Neurological assessment and/or any neuroimaging done post decannulation pre-hospital discharge

Of the 133 respondents, 50 (38%) performed routine neurological assessment (by ECMO physician or specialist in neurology) and 22 (17%) performed routine neuroimaging post-decannulation pre-discharge from the ECMO institution. Most centres (70%) did not offer any routine neuroimaging. A higher proportion of paediatric centres (n = 26, 65%) offered detailed neurological assessment pre-discharge compared to adult centres (p = 0.004). Routine neuroimaging was not offered in 45 (78%) adult centres or in 23 (66%) centres that treated both adult and paediatric patients (Table 3). Only 13 (10%) respondents reported ultrasound of the neck vessels after reconstruction.

Neurodevelopmental/neuropsychological out-patient follow-up post-hospital discharge

Table 4 shows the responses categorized by paediatric, adult and mixed adult and paediatric centres. Of 133 respondents, 65 (49%) offered routine out-patient follow-up for all or selected ECMO patients. This was more often offered by paediatric (73%) as compared to adult centres (40%). Of the paediatric centres (n = 40), 16 organized follow-up between 3 and 12 months, 6 centres followed this up at 12–15 months, 11 also checked at 15–36 months, 3 called for follow-up at 36 months to 4 years, 9 reviewed at pre-school (4–5 years of age), 4 at 6–8 years, 2 at 9–13 years and only 1 continued

Table 1. Neuromonitoring on ECMO.

Response	Total (n = 133)*	Paediatric centres (n = 40)*	Adult centres (n = 58)*	Mixed adult + paediatric centres (n = 35)*
Do you routinely use neuromonitoring in addition to bedside examination				
Yes, in all patients	57 (42.9)	29 (72.5)	9 (15.5)	19 (54.3)
Yes, only in selected patients	48 (36.1)	9 (22.5)	27 (46.6)	12 (34.3)
No, only bedside examination	14 (10.5)	1 (2.5)	13 (22.4)	0
Blank	14 (10.5)	1 (2.5)	9 (15.5)	4 (11.4)
Selected patient groups				
VA ECMO	33 (24.8)	4 (10)	21 (36.2)	8 (22.8)
ECPR	44 (33.1)	7 (17.5)	26 (44.8)	11 (31.4)
Post ANE	41 (30.8)	9 (22.5)	19 (32.7)	13 (37.1)
During circuit manipulations	5 (3.7)	0	3 (5.1)	2 (5.7)
Modality of neuromonitoring				
Intermittent EEG	52 (39)	14 (35)	23 (39.6)	15 (42.8)
Continuous EEG	19 (14.3)	4 (10)	6 (10.3)	9 (25.7)
aEEG	23 (17.3)	19 (47.5)	1 (1.7)	3 (8.6)
Cranial ultrasound	49 (36.8)	29 (72.5)	-	20 (57.1)
Transcranial Doppler	38 (28.6)	11 (27.5)	16 (27.5)	11 (31.4)
NIRS	88 (66.2)	32 (80)	28 (48.3)	28 (80)
Evoke potentials	20 (15.0)	3 (7.5)	13 (22.4)	4 (11.4)
Plasma bio-markers	33 (24.8)	3 (7.5)	19 (32.7)	11 (31.4)
Carotid Doppler	8 (6.01)	1 (2.5)	4 (6.9)	3 (8.6)
Routine neuroimaging on ECMO				
Yes	72 (54.1)	31 (77.5)	24 (41.7)	17 (48.5)
No	47 (35.3)	8 (20)	25 (43.1)	14 (40)
Blank	14 (10.5)	1	9 (1.7)	4 (11.4)

ANE: acute neurological event; ECPR: extracorporeal cardiopulmonary resuscitation; ECMO: extracorporeal membrane oxygenation; EEG: electroencephalogram; aEEG: amplitude-integrated electroencephalogram; NIRS: near infrared spectroscopy; VA: Veno-arterial.
*Numbers in brackets represent the calculated percentage of the total.

Table 2. Details on some of the neuromonitoring modalities on ECMO.

Response	Total (n = 133)*	Paediatric centres (n = 40)*	Adult centres (n = 58)*	Mixed adult + paediatric centres (n = 35)*
Routine use of EEG on ECMO (standard refers to the usual 30 minutes to 1-hour EEG)				
Standard EEG – daily	2 (1.5)	1 (2.5)	1 (1.7)	0
Interval EEG – once/twice/three times/week	8 (6.0)	2 (5.0)	1 (1.7)	5 (14.3)
EEG if suspicion of a seizure	56 (42.1)	21 (52.5)	23 (39.7)	12 (34.3)
EEG if cardiac arrest with/without ECPR	30 (22.6)	6 (15)	15 (25.9)	9 (25.7)
EEG if inability to evaluate subclinical seizures	32 (24.1)	15 (37.5)	8 (13.8)	9 (25.7)
We rarely/do not use	43 (32.3)	9 (22.5)	23 (39.7)	11 (31.4)
Continuous EEG				
Selected patient groups	8 (6.0)	6 (15)	1 (1.7)	3 (8.6)
Clinical suspicion of seizure/SE	21 (15.8)	10 (25)	4 (6.9)	7 (20)
Post CA with or without ECPR	11 (8.2)	5 (12.5)	2 (3.4)	4 (11.4)
NM blockade/subclinical	8 (6.0)	1 (2.5)	3 (5.2)	4 (11.4)
We rarely/do not use	85 (64)	23 (57.5)	44 (75.9)	20 (57.1)
NIRS				
NIRS throughout ECMO run as standard monitoring	66 (49.6)	27 (67.5)	16 (27.6)	23 (65.7)
NIRS during cannulation and circuit manipulations	4 (3.0)	1 (2.5)	2 (3.4)	3 (8.6)
NIRS if clinical concern of neurological problems	15 (11.2)	4 (10)	7 (12.1)	4 (11.4)

(Continued)

Table 2. (Continued)

Response	Total (n = 133)*	Paediatric centres (n = 40)*	Adult centres (n = 58)*	Mixed adult + paediatric centres (n = 35)*
NIRS if ANE	22 (16.5)	3 (7.5)	18 (31.0)	3 (8.6)
We rarely use NIRS	10 (7.5)	3 (7.5)	6 (10.3)	3 (8.6)
We do not routinely use NIRS	26 (19.5)	5 (12.5)	18 (31.0)	3 (8.6)
Plasma biomarkers of brain injury				
Pre-, post-cannulation, post decannulation	8 (6.0)	2 (5.0)	4 (6.9)	2 (5.7)
If clinical concern of neurological problems	23 (17.3)	4 (10)	13 (22.4)	6 (17.1)
Rarely	24 (18.0)	8 (20)	10 (17.2)	6 (17.1)
Plasma S-100B	23 (17.3)	9 (22.5)	9 (15.5)	5 (14.3)
NSE	50 (37.6)	9 (22.5)	29 (50)	12 (34.3)
We do not test	66 (49.6)	28 (70)	20 (34.5)	18 (51.4)
Evoke potentials				
Evoked potentials if clinical concern of neurological problems	34 (25.6)	11 (27.5)	17 (29.3)	6 (17.1)
We do not routinely use	72 (54.1)	24 (60)	29 (50)	19 (54.3)
Transcranial Doppler				
Intermittent TCD	13 (9.8)	9 (22.5)	1 (1.7)	3 (8.6)
TCD during ECMO cannulation and circuit manipulations	0	0	0	0
TCD if clinical concern of neurological problems	34 (25.6)	8 (20)	17 (29.3)	9 (25.7)
We do not routinely use TCD	58 (43.6)	18 (45)	26 (62.1)	14 (40)
Neuroimaging – cranial ultrasound if fontanelle open				
Yes	48 (36.1)	32 (80)		16 (45.7)
If clinical concerns	16 (12)	2 (5.0)	5 (8.6)	9 (25.7)
Daily cranial USS	20 (15)	14 (35)	1 (1.7)	5 (14.3)
Thrice weekly cranial USS	13 (9.8)	12 (30)		3 (8.6)
Twice weekly cranial USS	15 (36.1)	8 (20)		7 (20)
Cranial USS within the first 24 hours/clinical suspicion	8 (6.0)	3 (7.5)	1 (1.7)	4 (11.4)
Neuroimaging – CT scan brain				
CT Brain	47 (35.3)	9 (22.5)	24 (41.4)	14 (40)
Only if clinical concern of neurological problem	98 (73.7)	37 (92.5)	36 (62.1)	25 (71.4)
Routinely done on ECMO	15 (11.2)	0	11 (19)	3 (8.6)
No routinely neuroimaging	43 (32.3)	7 (17.5)	25 (43.1)	11 (31.4)
Reconstruction of vessels at decannulation				
Yes, always	38 (28.6)	22 (55)	7 (12.1)	10 (28.6)
Yes, in selected cases	47 (35.3)	12 (30)	19 (32.8)	16 (45.7)
No	34 (25.6)	5 (15)	23 (39.7)	5 (14.3)
Blanks	14 (10.5)	1 (2.5)	9 (15.2)	4 (11.4)

CA: cardiac arrest; CT: computed tomography; EEG: electroencephalogram; aEEG: amplitude-integrated electroencephalogram; ECMO: extracorporeal membrane oxygenation; ECPR: extracorporeal cardiopulmonary resuscitation; NM: neuromuscular; NIRS: near infrared spectroscopy; NSE; neuron-specific enolase; SE: status epilepticus; TCD: transcranial Doppler; USS: ultrasound scan.
*Numbers in brackets represent the calculated percentage of the total.

until adolescence. Only 15 (11%) had a structured longitudinal follow-up pathway (defined follow-up at regular intervals) versus 99 (74%) who reported no structured follow-up.

Figure 1 summarizes the distribution of responses with regard to routine neuromonitoring during ECMO and structured ECMO follow-up in ECMO centres in different parts of Europe. Figure 2 shows the distribution of paediatric, adult and mixed ECMO centres in the use of neuromonitoring (Figure 2(a)), type of neuromonitoring modality (Figure 2(b)), post hospital discharge out-patient follow-up (Figure 2(c)) and structured neurological or neuropsychological follow-up programme for ECMO patients post discharge (Figure 2(d)).

Future development of structured longitudinal neurodevelopmental/ neuropsychological follow-up

The majority of centres (n = 96, 72%) supported a longitudinal structured follow-up programme for all patients supported with ECMO. Paediatric centres

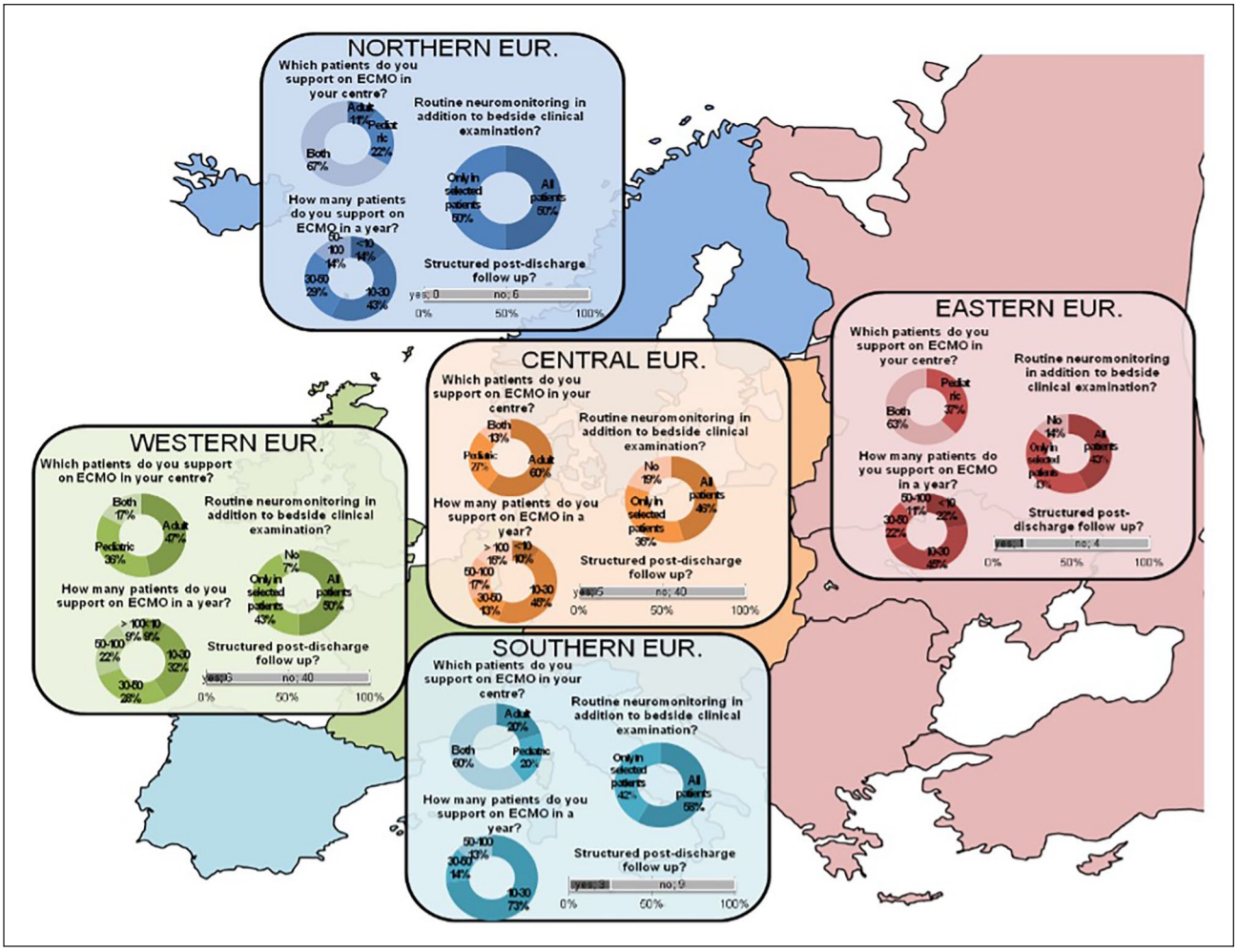

Figure 1. Map of Europe demonstrating differences in routine neuromonitoring during ECMO and post discharge follow-up. This is a graphical representation of ECMO centres within Europe (aggregated in different geographical parts of Europe). The circles within the individual boxes represent centre distribution with regard to type of patients supported, annual ECMO volume, use of routine neuromonitoring and structured follow-up post discharge.

showed a higher interest for this (93%) compared to 34 (59%) adult centres, and that follow-up should not be restricted to only those who had ANE, experienced ECPR or belonged to certain diagnostic categories like congenital diaphragmatic hernia or heart disease. Some comments reflected the lack of detailed information on the occurrence and severity of neurological impairment in adults and children over time. Most paediatric centres selected the Bayley Scales of Infant and Toddler Development, Wechsler Intelligence Scale for Children and Ages and Stages Questionnaire as neurodevelopmental/neuropsychological tests that are easily and routinely available. Other tests selected included Achenbach System of Empirically Based Assessment (ASEBA) Questionnaire including Adult Self-Report and Adult Behaviour Checklist (adult patient and carer versions) along with Quality of life (QoL). Furthermore, 94/133 (71%) agreed that there should be a minimum dataset for neurodevelopmental/neuropsychological follow-up of ECMO survivors, with 55/133 (42%) reporting that QoL questionnaire for adults and children should be included in this minimum dataset.

Submission of data to the ELSO Registry

Importantly, 93/133 (70%) expressed willingness to submit follow-up data to the ELSO Registry to enhance service development and provision. Centres that declined ($n = 14$) provided the following reasons: lack of clarity on the specifics of follow-up ($n = 6$), not being ELSO members/funding ($n = 5$), logistics – manpower ($n = 2$), and consent ($n = 1$) as barriers to submission of data.

Centre volume

There were no differences noted in this survey between annual ECMO case volume category (low

Table 3. Routine neurological assessment and imaging post ECMO pre-discharge.

Response	Total (n = 133)*	Paediatric centres (n = 40)*	Adult centres (n = 58)*	Mixed adult + paediatric centres (n = 35)*
Neurological assessment post ECMO pre-discharge				
Yes	50 (37.6)	26 (65)	12 (20.7)	12 (34.3)
No	63 (47.4)	13 (32.5)	33 (56.9)	17 (48.6)
Blank	20 (15)	1 (2.5)	13 (22.4)	6 (17.1)
Routine neuroimaging post ECMO pre-discharge				
Yes	22 (16.5)	13 (32.5)	3 (5.2)	6 (17.1)
No	93 (70)	25 (62.5)	45 (77.6)	23 (65.7)
Blank	18 (13.5)	2 (5)	10 (17.2)	6 (17.1)
Type of routine neuroimaging post ECMO pre-discharge				
Cranial USS	17 (12.7)	12 (30)	–	5 (14.3)
CT Brain	12 (9)	1 (2.5)	6 (10.3)	5 (14.3)
MRI Brain	17 (12.7)	12 (30)	1 (1.7)	4 (11.4)
USS of neck vessels if reconstructed	13 (9.8)	6 (15)	2 (3.4)	5 (14.3)
Timing of routine neuroimaging post ECMO pre-discharge				
Immediately after ECMO decannulation	9 (6.7)	4 (10)	4 (6.9)	1 (2.8)
In the first week after ECMO decannulation	17 (12.8)	8 (20)	4 (6.9)	5 (14.2)
Pre discharge from facility whichever is earlier	17 (12.8)	14 (35)	0	3 (8.5)
Hearing assessment at discharge				
Yes	20 (15.0)	16 (40)	1 (1.7)	3 (8.6)
No	90 (67.7)	21 (52.5)	46 (79.3)	23 (65.7)
Don't know/blank	23 (17.3)	3 (7.5)	11 (19)	9 (25.7)

ECMO: extracorporeal membrane oxygenation; CT: computed tomography; MRI: magnetic resonance imaging; USS: ultrasound scan.
*Numbers in brackets represent the calculated percentage of the total.

Table 4. Routine neurological assessment and imaging post hospital discharge as out-patient follow-up.

Response	Total (n = 133)*	Paediatric centres (n = 40)*	Adult centres (n = 58)*	Mixed adult + paediatric centres (n = 35)*
Post hospital discharge out-patient follow-up				
Yes, for all ECMO patients	31 (23.3)	16 (40)	12 (20.7)	3 (8.6)
Yes, for selected patient populations	34 (25.6)	13 (32.5)	11 (19)	10 (28.6)
No	48 (36.1)	8 (20)	25 (43.1)	15 (42.9)
Blank	20 (15.0)	3 (7.5)	10 (17.2)	7 (20)
Timing of the first post hospital discharge out-patient follow-up targeted at neurology/neurodevelopment				
Within first 4 weeks of discharge	14 (10.5)	4 (10)	4 (6.9)	6 (17.1)
2–3 months after discharge	22 (16.5)	11 (27.5)	7 (12.0)	4 (11.4)
4–6 months after discharge	7 (5.2)	3 (7.5)	4 (6.9)	0
6–12 months after discharge	5 (3.8)	1 (2.5)	4 (6.9)	0
1 after discharge	4 (3.0)	1 (2.5)	3 (5.1)	0
2 years after discharge	0	0	0	0
Other (specify)/blanks	10 (7.5)	8 (20)	1 (1.7)	1 (2.8)
Blank	17 (12.8)	2 (5)	9 (15.5)	6 (17.1)
Structured neurological or neuropsychological follow-up programme for ECMO patients post discharge (a pathway where multidisciplinary follow-up and regular intervals are in place) within the ECMO institution				
Yes	15 (11.2)	10 (25)	3 (5.1)	2 (5.7)
No	99 (74.4)	27 (67.5)	45 (77.5)	27 (77.1)
Blank	19 (14.2)	3 (7.5)	10 (17.2)	6 (17.1)

(Continued)

Table 4. (Continued)

Response	Total ($n = 133$)*	Paediatric centres ($n = 40$)*	Adult centres ($n = 58$)*	Mixed adult + paediatric centres ($n = 35$)*
Should there be longitudinal structured follow-up programme?				
Yes	96 (72.2)	37 (92.5)	34 (58.6)	25 (71.4)
No	8 (6.0)	0	7 (12.1)	1 (2.8)
Don't know/unsure	12 (9.0)	1 (2.5)	8 (13.8)	3 (8.6)
Blank	17 (12.8)	2 (5)	9 (15.5)	6 (17.2)
What should an ideal follow-up programme?				
Yes, should be longitudinal for ALL irrespective of diagnosis, age, or ANE	96 (72.2)	36 (90)	33 (56.9)	26 (74.3)
Yes, should be targeted to those who have had neurological issues on ECMO	13 (9.8)	1 (2.5)	10 (17.2)	1 (2.9)
Yes, should be targeted to certain diagnosis (for example: CDH)	4 (3.0)	0	3 (5.2)	0
Yes, should be targeted to ECPR or if they have had cardiac arrest peri-ECMO	11 (8.2)	0	9 (15.5)	1 (2.8)
Other than above	6 (4.5)	1 (2.5)	3 (5.2)	1 (2.8)
Should there be a minimum dataset of neurodevelopmental/neuropsychological follow-up of ECMO survivors				
Yes	94 (70.7)	34 (85)	36 (62)	24 (68.6)
No/don't know/other	22 (16.5)	4 (10)	13 (22.4)	5 (14.3)
Blank	17 (12.8)	2 (5)	9 (15.6)	6 (17.1)
Would your institution be willing to submit follow-up data to ELSO to enhance service development and provision?				
Yes	93 (70)	31 (77.5)	37 (63.8)	25 (71.4)
No	9 (6.8)	0	7 (12.1)	2 (5.7)
Other	14 (10.5)	7 (17.5)	5 (8.6)	2 (5.7)
Blank	17 (12.8)	2 (5)	9 (15.6)	6 (17.1)

ANE: acute neurological event; ECMO: extracorporeal membrane oxygenation; CDH: congenital diaphragmatic hernia; CT: computed tomography; MRI: magnetic resonance imaging; USS: ultrasound scan.
*Numbers in brackets represent the calculated percentage of the total.

volume <30 cases/year and high volume >30 cases/year), see Table 1, Supplemental Digital Content 2 (Additional File 2).

Discussion

This study, conducted under the EuroELSO Neurological Monitoring and Outcome Working Group, is the first cross-sectional, multi-institutional, international survey on neurological monitoring on ECMO and neurocognitive outcome follow-up of ECMO survivors. This descriptive work reports responses from a large group of ECMO centres providing care for children and adults, both cardiac and respiratory ECMO, including ECPR and bridging to transplant services. Approximately 44% of the participants represented high volume (>30 ECMO cases/year) centres. Given the diversity of countries and organizational networks within each country, a response rate of 63% (133/211), particularly with a mix of ELSO and non-ELSO centres, is representative of ECMO provision in Europe, and is higher than previously published surveys on ECMO.[35,36] We captured a significant proportion of the ECMO centres, notwithstanding the logistical barriers including language and lack of a comprehensive directory of all ECMO providers in Europe. The neuromonitoring modalities were intentionally kept broad as it is well acknowledged that no single modality can reliably provide the necessary information and that variability between centres is wide.[18] Intermittent and continuous modalities were included knowing that some are highly resource-dependent and not easily available, and questions were directed towards monitoring of specific sub-groups.

Important findings from the survey and how we can use them?

Neuromonitoring, neuroimaging and follow-up. The approach to neuromonitoring, neuroimaging modalities and neurological follow-up varied within the participating centres and within adult, paediatric and mixed centres across Europe. The majority (79%) reported regular neuromonitoring in addition to bedside neurological examination. Less than half (43%) routinely monitored all patients regardless of neurological risk factors while 36% only monitored selected

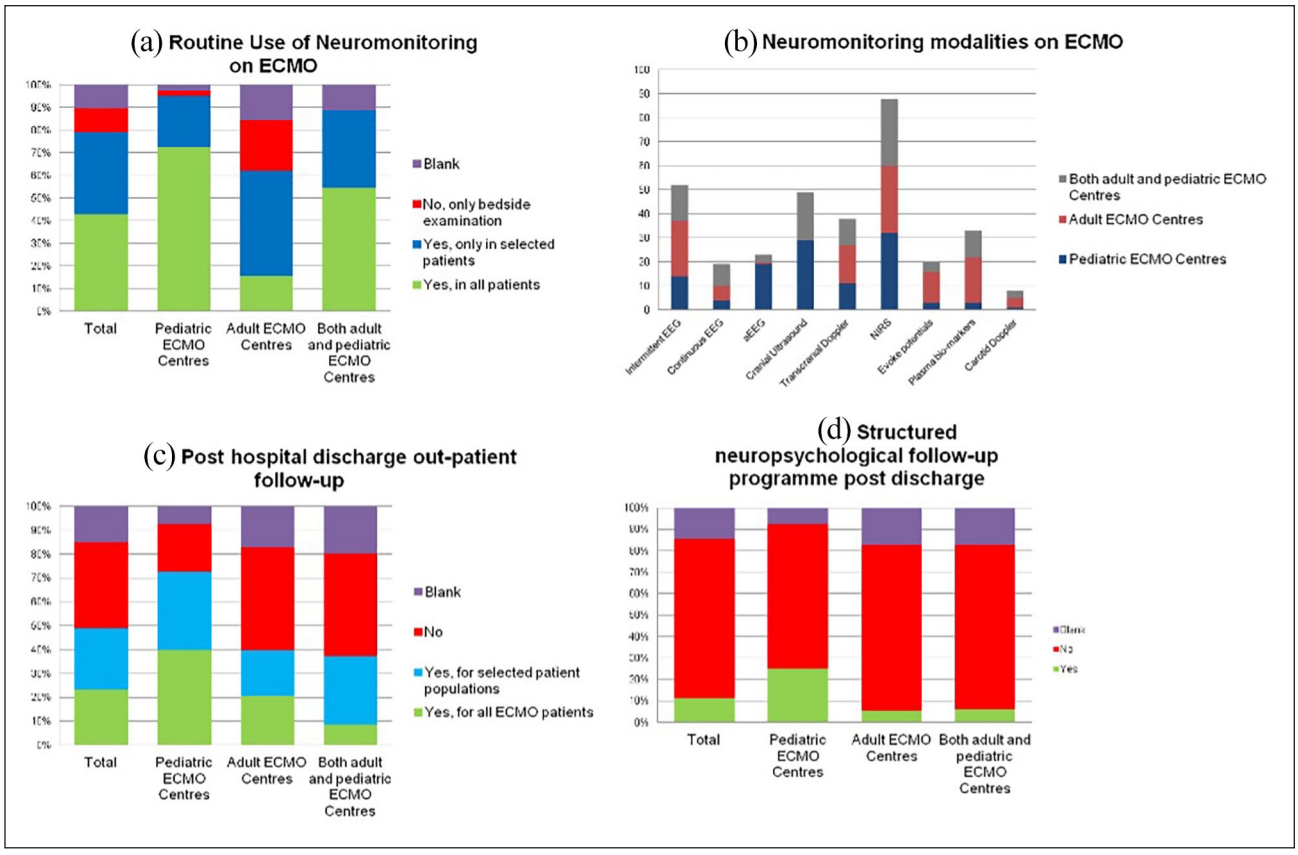

Figure 2. Distribution of ECMO centres in the use of neuromonitoring, neuromonitoring modalities used, and post ECMO follow-up. Distribution of paediatric, adult and mixed (looking after both adult and paediatric patients) ECMO centres in the use of neuromonitoring (a), type of neuromonitoring modality (b), post hospital discharge out-patient follow-up (c) and structured neurological or neuropsychological follow-up programme for ECMO patients post discharge (d).

patients. NIRS was the most selected neuromonitoring modality, despite the fact that monitoring protocols and thresholds for intervention are not universally available nor accepted in children[37] or in adults. NIRS being a non-invasive, bedside, continuous tool with easy application of sensors and readable display, makes it highly favourable in ECMO patients.[38–40] Reliability and reproducibility remain a concern during ECMO, particularly signal pathlength and haemoglobin concentration in the setting of haemodilution.[41] While the NIRS values may change rapidly with changes in patient condition and ECMO flows, a change in trend is of greater value than the absolute number.[42,43] Routine intermittent EEG was used in children more often than in adults, but both paediatric and adult centres reported clinical concerns as the significant driver for requesting an EEG. Very few centres overall performed aEEG, evoked potentials, continuous EEG or carotid Doppler, but some centres, predominantly adult centres, reported using serum brain injury biomarkers. Although the yield is better on prolonged or continuous EEG as reported in paediatric ECMO, it is restricted by availability of resources.[44–46] Seizures – clinical or subclinical remain a concern on ECMO[6,44] and use of neuromuscular blockade may mask identification of seizures, thus having some form of intermittent or continuous EEG monitoring is desirable. Furthermore, abnormal background electrical activity and organization can indicate an encephalopathic process as reported by Sinnah et al.[47] on adult patients supported on VA ECMO who also described lack of sleep transients in continuous EEG as a marker of poor neurologic prognosis.

Cranial USS was the most common (67%) neuroimaging modality in the centres treating children with variability in frequency of cranial USS. Very few centres (mainly adult centres) routinely performed brain CT scans, the main impetus remained a new clinical neurological concern. Fifty percent of all respondents perform routine neurological assessment after decannulation before discharge, and neuroimaging (cranial USS, CT brain and MRI brain) as part of this evaluation was included in 22% of the centres. Paediatric centres approached post-decannulation neurological assessments differently to adult centres: two-thirds (65%) offered neuro-assessment compared to one in five (21%) adult centres, perhaps explained by the long-term studies

on neonatal ECMO survivors showing early and late deficits in neuropsychological outcomes.[31–33] A single centre adult ECMO survivors ($n = 28$) study reported impaired neuropsychological performance (41%), neuroradiological findings (52%), and pathologic EEG (41%) at an average of 5 years after ECMO, and further that cognitive function correlated to neuroimaging findings.[29] Despite the awareness that both paediatric and adult ECMO survivors have significant neurodevelopmental/neuropsychological needs, interestingly, in our survey, only 11% centres had structured neurological or neuropsychological multidisciplinary follow-up programme.

Optimal targets for neuromonitoring and correlation with long-term outcomes in ECMO survivors

There are currently no widely accepted neuromonitoring targets that correlate with long-term outcomes in either adults or children. Reductions in NIRS measurements have been associated with unfavourable outcomes in children[48] and adults.[39,49,50] TCD permits the assessment of abnormal cerebral flow patterns on ECMO that may be associated with neurological complications,[51–53] and may be useful in detecting micro-emboli in real time, however the clinical utility remains uncertain.[54] Monitoring of elevated brain injury bio-markers has been described in ECMO patients, but the routine use is yet to be justified.[55–57] A recent publication reported that in post-CPR adults on ECMO, NSE levels measured at 24 hours can be used to assess the neurologic outcome with improved specificity if measured serially.[58] Correlation between neuroimaging and outcome are well-described in both paediatric and adult patients; while routine CT scanning remains resource intensive, when clinically indicated has a high yield and permits modification of anticoagulation which, in turn, may change outcome.[17,59,60] It is important to bear in mind that even multimodal neuromonitoring strategies may limit the ability to detect neuro-injury in real-time. Once detected, clinicians are able to target haemodynamic and anticoagulation management so as to minimize any secondary neurological injury. Anticipatory monitoring in certain high-risk situations such as femoral V-A ECMO cannulation to detect regional differences (NIRS), monitoring and treating seizures (continuous EEG), and lightening of sedation to permit better clinical assessment of neurological state. While neuromonitoring may not always translate into better outcomes, it offers an opportunity to individualize care, prevent progression, and support taking important decisions like re-direction of care in the event of devastating neurological injury.

While many aspects of mitigating neurological injury on ECMO are not necessarily modifiable, one must ensure that modifiable factors such as avoiding rapid shifts of CO_2 at initiation of ECMO, rigorous management of anticoagulation and inspection of the circuit for any potential thromboembolic material should be protocolized and strictly followed.[61,62] Tools to identify thrombo-embolic material accumulating on the internal surfaces of the ECMO circuit and oxygenator are not reliably available, however vigilance for increased membrane pressures should be maintained and treated promptly.[62]

The question of follow-up – who, when, how?

The high level of consensus amongst the respondents for structured follow-up supports the need for early and late long-term follow-up for children and adults supported on ECMO. The EOLIA Trial did not report a higher incidence of neurological events in the ECMO supported adults,[63] nor did the CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory Failure) trial demonstrate a difference in severe disability of any measure of health care quality between patients randomized to ECMO versus controls 6 months after randomization.[64] However, recent literature has identified that ECMO survivors frequently experienced physical complications, functional limitations, anxiety, depression and post-traumatic stress symptoms with worse outcomes in those supported on VA ECMO and better long-term QoL in those supported on veno-venous (VV) ECMO and improvements noted over time.[30,65,66] Sequential longitudinal follow-up from the Netherlands neonatal ECMO follow-up programme at 5, 8 and 17 years have reported significant impairment in specific neuropsychologic skills in adolescence (attention, memory, executive functioning, visual-spatial functions, social-emotional functioning and behaviour), all with potential impact on learning and academic performance.[31–33,67] Some of the adult ECMO survivors have been described to develop psychiatric disorders such as organic mental, obsessive-compulsive including post-traumatic stress disorders.[29,30,68]

This survey may provide key information for a follow-up protocol. The majority of respondents (96, 72%) agreed that such a programme should be longitudinal and should include all ECMO survivors irrespective of diagnosis, age or neurological events. The availability of neurodevelopmental/neuropsychological testing was variable between countries. This highlights the need for different follow-up models organized as regionalized follow-up accounting for local and regional factors. Furthermore, 70% agreed that there should be a minimum dataset for neurodevelopmental/neuropsychological follow-up: 41% proposed a QoL questionnaire, whereas a third reported unfamiliarity with tests.

Measurement of QoL appears to be well established and used in several paediatric[69–72] and adult[65,68] follow-up studies. Early intervention by identification and management of physical and mental health problems may improve the QoL outcomes. As increasingly recognized from studies on neonatal ECMO survivors, intelligence tests alone do not identify those at risk for academic problems.[71,72] Thus, a follow-up programme focussed on long-term, problem-oriented neurocognitive assessment with a universally accepted minimal dataset and provision for local and regional variations, may help the adult and paediatric ECMO survivors.

Should neuroimaging be part of the follow-up?

There is not enough evidence that neuroimaging alone, on ECMO or after ECMO, can be used to predict outcome. Neuroimaging abnormalities are more frequent in VA than in VV ECMO and are associated with cognitive impairment.[3,6,8,30,38,66,73–75] Early studies in neonates have shown that neuroimaging scores were significantly worse in survivors with delayed development, and that survivors with non-haemorrhagic abnormalities had a higher risk of delayed development than those with isolated haemorrhagic abnormalities (39% vs 21%). The value of MRI post ECMO is not fully elucidated. In paediatric survivors, MRI identified significantly more abnormalities compared to routine cranial USS.[76,77] Rollins et al.[76] found that neither MRI nor cranial USS correlated with neurodevelopmental outcome using Bayley scales and the best predictor of neurologic impairment was feeding ability at discharge. However, the role of early neuroimaging would be to assign risk categories for neurocognitive outcome.[77,78]

Adult studies correlating findings on brain MRI early after decannulation and outcome are limited.[79] A long-term follow-up study (median 9 years after discharge) showed cerebrovascular lesions on MRI scans in 37% (14/38 patients) and seen most commonly in the group treated with VA ECMO (7/11, 64%) and correlated with poor memory and executive function.[27] Uniformity on interpretation and reporting neuroradiological findings are an important primary first step that influences our understanding of how findings correlate with outcome.

A pragmatic approach to neuromonitoring and neurological follow-up

Whilst it is ideal that all on ECMO should receive full continuous monitoring, it may not be logistically feasible, and aiming for 'good/optimum' rather than 'perfect' may be a pragmatic solution. Individual institutions need to develop guidelines as per local availability and resources: however, some principles remain. These principles include identifying children or adults at risk (significant hypoxaemia or hypotension or shock or acidosis, cardiac arrest pre-ECMO, ANE on ECMO), avoiding rapid fluctuations in $PaCO_2$ on initiation of ECMO, daily regular bedside assessments, minimizing sedation and promoting awake ECMO to help with early detection, a low threshold for investigations if any neurological concerns. It is important to keep in mind that each neuromonitoring modality has caveats and pitfalls which need to be understood.[38] A neurological assessment pre-discharge from ECMO centre should be a minimum standard. Neuroimaging – preferably MRI of the brain – should be considered in those who are in the high-risk category (as above), who have had an ANE on ECMO,[7,15] VA ECMO,[2,5,80] ECPR[20,22] and any major complication on ECMO with an aim to identify any unrecognized injury and aid categorizing follow-up pathways.

Neurological follow-up will vary for children and adults in different countries, heavily influenced by local, regional and national policies and funding structure. Respondents favoured a minimum dataset and chose QoL measure. Health related QoL measures have been described in ECMO survivors.[4,19,65,68,81] It is beyond the scope of the current work to determine the best protocol to adopt. Nonetheless, neurological examinations such as modified Rankin scale or similar assessments could be considered. Commonly used instrument in children is the Paediatric Quality of Life – Peds QL.[70,82–84] Furthermore, bleeding and thrombotic events during ECMO were associated with worse outcomes assessed by the Paediatric Overall Performance Category, and the Paediatric Cerebral Performance Category. The incidence rates per 100 ECMO days of bleeding and thrombotic complications may be alterable with standardized and rational management of anticoagulation, ECMO circuitry and patient care practices.[85] Investing in long-term follow-up programme can be an important component of the patient's journey to improved health,[72] and multidisciplinary follow-up can be particularly helpful for rehabilitation[86] particularly in ECPR survivors. Limited long-term neurologic and neurodevelopmental outcome after ECPR data are available from several single institution series; however, data on the long-term follow-up of adult ECMO survivors is currently not available. The high level of agreement to submit objective follow-up data to the ELSO Registry, if clearly defined, was very encouraging; and will inform the future projects of consensus development within the EuroELSO Working Group.

Limitations

A potential bias may be introduced as respondents may be different from those who chose not to respond. It was difficult to identify all European ECMO centres and

there is a chance that some centres have not been invited to participate in survey. Despite that, the centres that participated included major low-, medium- and high-volume programmes and additional centres from their networks representing the majority of ECMO cases performed in each country, with the exception of Greece and Poland, where no ECMO centre participated. There might be variations in neuromonitoring modalities in different centres and countries due to non-clinical factors, including financial, historical and local expertise. However, exploring these were beyond the scope of this survey. Furthermore, neurological/neurodevelopmental follow-up is highly dependent on funding streams within each country.

Conclusions

This international survey suggests that while neuromonitoring is routinely undertaken in many centres, the practice as to who should be monitored, when and what modality should be used are unclear. A standardized monitoring set and threshold will benefit clinicians to compare approaches and outcomes in a homogenous manner and help progress our understanding and prevention/mitigation of complications. The respondents strongly supported follow-up, and the development of a standardized set of outcome measures and what to ask survivors, will be of significant benefit. There is an important need for more follow-up neuroimaging correlated with neurological, cognitive and psychiatric outcomes. The survey demonstrates wide variability in practices largely influenced by institutional preferences, resource availability and the international, national and local variations in the configuration of primary, secondary and tertiary healthcare services that provide follow-up. Hence, guidelines advocating a standard may be of benefit. International consensus on neuromonitoring modalities and guidelines for long-term longitudinal follow-up endorsed by the EuroELSO may support individual institutional practices. Our survey findings would inform such a consensus development.

Ethics approval and consent to participate

As this was a service delivery quality improvement project. Ethical approval was waived. All data generated and/or analysed during this current study are included in this published article and supplementary information files.

Availability of supporting data

Data available on request from the authors

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